Claim 29 (previously presented): A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a fusion protein of claim 27.

Claim 30-39 (cancelled).

REMARKS

Claims 5, 8-9, and 11-39 are pending in this application. Claims 8, 9, and 11-21 were withdrawn from consideration on May 21, 2002, solely in response to the restriction requirement imposed in the Office Action dated March 22, 2002. Applicants have expressly reserved the right to prosecute the nonelected claims in another application. Claim 5 has been allowed. Claims 30-39 are hereby cancelled.

Claim Rejections: 35 U.S.C. § 112

The Examiner rejected claims 22-25 and 27-29 under 35 U.S.C.§ 112, ¶ 1, on grounds that the specification, while being enabled for fusion proteins comprising amino acids 1-160 of SEQ ID NOs: 8 and 9, is not enabling for "homologues, equivalents, or variants of those sequences." The Examiner maintains that it would require undue experimentation for one of ordinary skill in the art to determine functional fusion proteins within the scope of the claims, and that it would be unpredictable whether proteins with a homology as low as 60% would bind to TGFβ.

The Examiner has also rejected claims 22-25 and 27-29 under 35 U.S.C.§ 112, ¶ 1 on grounds that the specification does not describe adequately "native molecules" or "naturally occurring variants" within the scope of those claims.

Applicants respectfully disagree with these contentions, but in the interests of expediting prosecution have amended claims 22 and 27 to particularly point out that the claimed TGF-β RII fusion proteins comprise a biologically active amino acid sequence which corresponds to all or all part of the extracellular region of native TGF-β RII and which is at least 90% homologous to SEQ ID NOs: 8 or 9, or equivalents thereof. The substantial homology of the specified amino acid sequences to those of SEQ ID NOs: 8 and 9 obviates any concern that those of ordinary skill would need to undertake undue experimentation to determine functional fusion proteins within the scope of the claims.

Support for these amendments is found, e.g., at page 28, lines 7-9 of the specification as originally filed.

Additionally, all of claims 22-25 and 27-29 as amended satisfy the statutory written description. Applicants have recited a representative number of sequences within the genus of the claims (*see, e.g.*, specification page 29, lines 16-19) and have also provided a recitation of structural features common to a substantial number of the members of that genus (*see e.g.*, specification, page 26, lines 15-33, and page 27, lines 1-17). *Regents of the University of California v. Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997).

Accordingly, applicants respectfully request that the Examiner withdraw her rejections of claims 22-25 and 27-29 under Section 112.

Claim Rejections: 35 U.S.C. § 103

The Examiner has rejected claims 22-26 and claims 28-29 under 35 U.S.C. § 103(a) ("Section 103(a)") as being unpatentable as obvious in light of U.S. Patent No. 6,046,157 ("*Lin*") in view of U.S. Patent No. 5,605,690 ("*Jacobs*").

Per the Examiner, it would have been obvious to combine *Lin's* disclosure that amino acids 1-166 of SEQ ID NO: 8 (*Lin*, column 9, lines 13-19) can be used as a soluble receptor that binds to TGF-β and *Jacobs's* disclosure of fusion proteins with a soluble TNF receptor and IgG1 (*Jacobs*, column 7, lines 41-58). The motivation to make this combination, according to the Examiner, was provided by *Lin's* mere disclosure that TGF-β receptors are useful and *Jacobs's* disclosure that single chimeric antibodies having TNFR displayed bivalently and *may* have enhanced binding affinity for the TNF ligand.

It is inconsistent for the Examiner to maintain that claims 22-25 and 27-29 are not enabled (*see* October 17, 2003 Office Action, page 4: "[t]he amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation" ), and yet posit that *Jacobs's* equivocal statement that chimeric antibodies having TNFR displayed bivalently and *may* have enhanced binding affinity

would have led those of ordinary skill to modify *Lin* to make Applicants' TGF-β fusion proteins. The unpredictability cited by the Examiner in her Section 112 rejections would have precluded the skilled artisan from assuming that such a modification of *Lin* in light of *Jacobs* would work.

Further, *Jacobs* is prior art to *Lin*. *Lin* sought to modulate the effects of TGF-β *in vivo* (see, e.g., column 9, lines 59-67 and column 10, lines 1-13), yet never resorted to fusion proteins that expressed bivalently in an effort to enhanced binding affinity. The Examiner admits that "the *Lin* patent fails to teach fusion proteins." (October 17, 2003 Office Action, page 5). Given the availability of *Jacobs* to the *Lin* inventors, and the objects of the *Lin* invention, this failing by *Lin* to disclose fusion proteins undercuts the notion that those of skill in the art would have modified *Lin* on the basis of *Jacobs*.

Applicants respectfully submit that the Examiner has still not provided the requisite rigorous showing of a clear and particular suggestion, teaching, or motivation to combine *Lin* and *Jacobs* to yield the claimed TGF-β RII/Fc fusion proteins. *In Re Dembiczak,* 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). Applicants maintain that there is no adequate basis to support a conclusion that those of skill in the art would have combined *Jacob's* disclosure regarding TNFR chimeric antibodies with *Lin* to render the claimed inventions obvious. *Hybritech Inc. v. Monoclonoal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). The unpredictability of amino acid sequence structural and functional properties referenced by the Examiner in the context of enablement meant that there would have been no reasonable expectation that such a combination or modification would have proved successful. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Accordingly, Applicants respectfully request that the Examiner withdraw her rejections of claims 22-26 and claims 28-29 under Section 103.

In light of all of the foregoing, it is respectfully maintained that claims 22-29, like claim 5, are allowable and that all of those claims should be passed to issue.

Respectfully submitted,

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Date: December 23, 2003